Stem cells in dermatology*

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Abstract: Preclinical and clinical research have shown that stem cell therapy could be a promising therapeutic option for many diseases in which current medical treatments do not achieve satisfying results or cure. This article describes stem cells sources and their therapeutic applications in dermatology today.
Keywords: Adult stem cells; Dermatology; Hematopoietic stem cells; Stem cells; Regenerative medicine

INTRODUCTION

The current trend in medicine is to focus on two major areas in which until recently there was not much emphasis on: "prevention" of diseases and "regenerative medicine". The first provides the power to change an individual's destiny, preventing a disease from occurring and increasing life expectancy, while the second is an attempt to cure diseases for which modern medicine has yet no treatment available. This article aims to briefly address regenerative medicine, with the theme "stem cells", from its discovery to its current applications and future prospects, describing the important role of skin cells in this context.

ORIGIN AND CONCEPTS

Bone marrow transplantation for hematologic diseases occurs since the 1950s.[1] It was known then, that there was a type of cell within the bone marrow that could give rise to all lineages of blood cells, determining the success of this treatment.[1] Thus emerged the first concept of a primitive cell that specialized to generate other cells with specific functions. At the end of the 90s, came the first evidence that, faced with different stimuli and environments, this hematopoietic progenitor cell could generate cells that differed from the original tissue (plasticity) and that they were attracted to damaged tissues distant from their surroundings.[2,3,4,5] Cells that presented this behavior were named stem cells.

For a cell to be considered a stem cell, it has to present three characteristics: self-renewal, i.e., asymmetric division resulting both in cells that are similar to it, as well as specialized cells; the ability to regenerate the tissue in which it is located, and plasticity, that is the ability to generate other cell types, different from those of the original tissue.[6]

From the moment that stem cells were discovered in bone marrow, the search for other sources began. Fundamentally, stem cells are present in various body tissues, from the embryo to the adult individual, since all tissues have some degree of repair capacity.[7] One of the most comprehensive classifications divides them in two groups: embryonic stem cells present in the blastocyst, the inner cell mass of an embryo five days after fertilization of the egg by the sperm; and adult stem cells present from the formation of the fetus and responsible for repairing injured tissues composed of cells in more specialized stages

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(Figure 1). [8,9,10,11] Amongst adult stem cells there are two types that differ in their origin and differentiation capacity: the aforementioned hematopoietic stem cells, originally derived from bone marrow that give rise to all hematopoietic tissues, and mesenchymal stem cells pre-determined to differentiate into various cell lineages of mesodermal origin such as osteogenic, chondrogenic and adipogenic lineages, and cartilage and bone tissues.[10,11,12] These cells have a significant role in tissue repair, homeostasis and immunomodulation. Some tissues are rich in mesenchymal stem cells and are easily harvested, such as the adipose tissue, dermis, bone marrow and umbilical cord tissue, including Wharton's jelly.[13,14] Both types of adult stem cells, despite having a pre-determined differentiation into certain tissues, demonstrated *in vitro* ability to transform, among others, into neuronal, hepatic, and muscular tissues. Mesenchymal stem cells are included in more than 200 clinical trials for various diseases like diabetes, ulcerative colitis, systemic lupus erythematosus, dilated cardiomyopathy, cirrhosis, spinal cord injury, and osteoarthritis to cite a few. Hematopoietic stem cells, from bone marrow and umbilical cord blood, are being evaluated for hematologic and non-hematologic diseases in over 3,000 clinical studies with protocols registered in the United States National Institute of Health Program ClinicalTrials.gov (www.clinicaltrials.gov).

MAIN SOURCES OF ADULT STEM CELLS

Organs that have a significant degree of cell turnover, such as bone marrow and skin, have a tendency to present cell populations richer in stem cells.

Alternatives for easy retrieval and storage of hematopoietic stem cells in high concentration are the bone marrow and umbilical cord and placental blood, the latter being the only form to collect in which there is no need for surgical intervention, since it is drawn after clamping the umbilical cord concomitanlty or after the manual removal of the placenta.[11] There are several advantages described for stem cells derived from cord blood, such as lower viral disease transmission's incidence, high regenerative power and low immunogenicity, all secondary to the time of birth when there is less exposure to external agents and the fact that the newborn is immunologically immature.[15] Bone marrow, adipose tissue, dermis and umbilical cord tissue are all sources with high concentration of mesenchymal stem cells.[16] Among these, we highlight the umbilical cord tissue, which can be collected in a

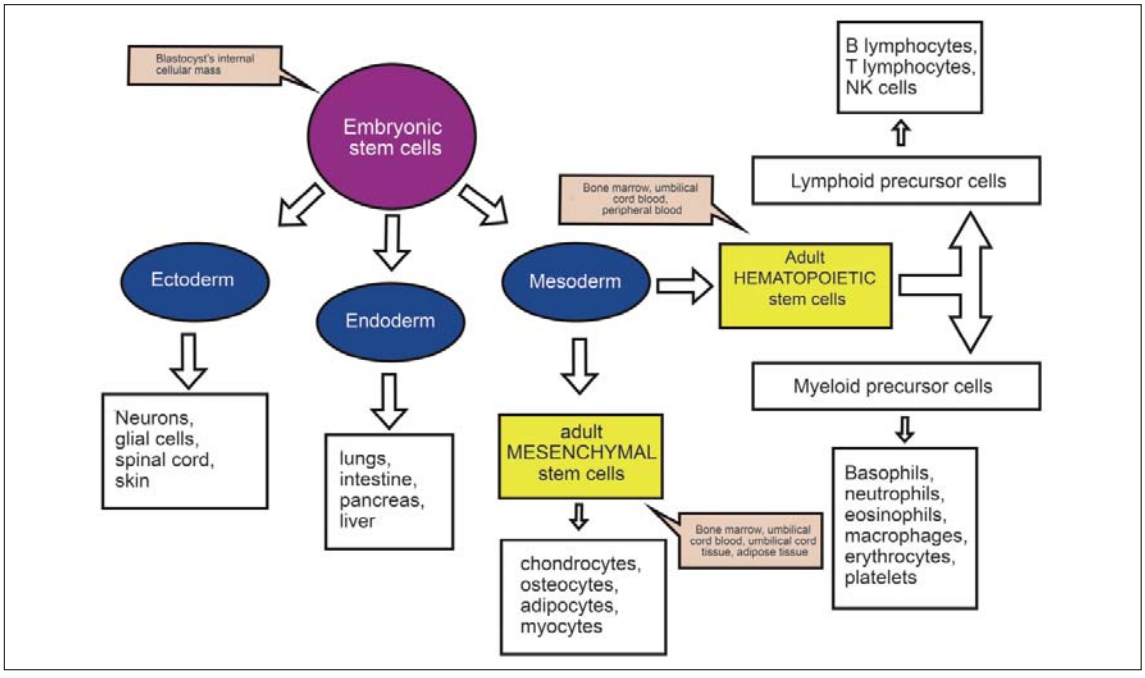

Figure 1: Origin of adult human tissues from embryonic stem cells. Differentiation and maturation of cells can occur in the embryonic and adult periods. Embryonic stem cells can originate tissues from all three germ layers. The mesodermal layer produces mesenchymal and hematopoietic precursor cells. Adult tissues have natural stocks of resident stem cells, and in the cellular differentiation cascade there are cells going to undescribed differentiation processes. The main sources of embryonic and adult stem cells for therapeutic purposes are presented below

non-invasive manner, and has cellular regenerative potential comparable to the regenerative power of the skin of a very young individual.[13]

Until the present, only hematopoietic stem cells from bone marrow and umbilical cord blood are authorized for medical use. They may be used in hematological, genetic or acquired diseases, and also some common childhood tumors such as neuroblastoma, retinoblastoma, Wilms' tumor, and osteosarcoma.[17]

STEM CELLS AND SKIN

The skin, being an organ of great cell replication, has several groups of stem cells present in its layers.

Interfollicular stem cells are found in the epidermis, near the basal membrane. Their primary role is to repair epidermal trauma. In the hair follicle's histologic complex there are follicular, sebaceous and neural crest stem cells. Follicular and neural crest stem cells cohabit in the bulge. In the sebaceous gland, we can find sebaceous stem cells.[18,19]

Stem cells within the dermis, adipose tissue and hypodermis are essentially of mesodermal origin, therefore mesenchymal. They are closely associated with blood vessels and generate fibroblasts and myofibroblasts that participate actively in repair mechanisms. Mesenchymal stem cells have a strong link with repair and regeneration processes in soft tissue, musculoskeletal and vascular systems.[20,21]

There is still no definite pattern, which can prioritize and define exactly what degree of importance a cell has, compared to another, in the skin repair mechanism. However it is known that, there is a marked interplay between systems through molecular interactions, such as the cells of the hypodermis presenting paracrine action over dermal fibroblasts. Mesenchymal stem cells located in the dermis and hypodermis are critical in this process because they coordinate the response of tissue repair by recruiting other host cells, growth factors and extracellular matrix secretory proteins.[12,22]

ROLE OF CUTANEOUS STEM CELLS IN THE REGENERATION OF OTHER TISSUES

Cutaneous stem cells have been experimentally explored, in several animal models and *in vitro*, to demonstrate their potential and plasticity, especially because the skin is an inexhaustible source of stem cells that are easy to obtain; besides being autologous cells, thereby avoiding complications such as graft-versus-host disease.

Due to the ontologic proximity between neural tube stem cells and follicular complex's neural crest cells, they may be used in cell therapy for spinal cord injuries. Sieber-Blum from the University of Newcastle, in a trial with mice, observed an improvement of 24% in sensitivity and perception of touch in the lower limbs after induced spinal cord injuries.[23] Although cell transplantation was performed unilaterally, improvements were bilateral, suggesting that genes from epidermal neural crest cells encode and express neutrophins, and trophic and angiogenic factors, that justify bilateral functional improvements. Recently, researchers from the same center demonstrated the multipotentiality of human epidermal cells form the neural crest, through the isolation, characterization and *ex-vivo* expansion, transforming them into osteocytes and melanocytes, thus identifying a source of easy access and great power of differentiation.[24,25]

Mesenchymal stem cells from human dermis have also shown great power of expansion *in vitro*, especially when collected from newborns. Their easy obtainment, multiplication and security, seen in population doublings in culture, strongly suggests that in the future they may be conveniently used for the regeneration of tissues, such as adipose, muscle and osteogenic.[26]

Since 2006, dermal fibroblasts have been manipulated *in vitro* and genetically reprogrammed to regress to an immature and undifferentiated state that precedes their current state of differentiation; afterwards they were induced to develop into various cell lines. These immature cells produced *in vitro*, derived from fibroblast regression, are called induced pluripotent cells (iPS).[27]

Surprisingly, dermal fibroblasts themselves have also demonstrated characteristics of *in vitro* pluripotency, without the need to be induced to immaturity by the activation of embryonic stage genes. Canadian researchers obtained a hematopoietic progenitor cell from a fibroblast through the application of specific cytokines. This hematopoietic precursor cell, developed *in vitro*, was able to generate granulocytic, monocytic, megakaryocytic and erythroid lineages, besides demonstrating the ability to repopulate the bone marrow by grafting.[28]

INDUCED PLURIPOTENT CELLS *(iPS)*

As described earlier, skin cells have a significant role in stem cell studies, particullarly in the retrieval of induced pluripotent cells, which are an alternative to using embryonic stem cells or therapeutic cloning in research.

In 2006, Japanese researchers genetically reprogrammed cells from mouse tail, so that they reverted to the behaviour of embryonic stem cells. This reprogramming process occurs through the insertion of a virus containing four genes. These genes are inserted into the DNA of an adult cell (e.g. skin cell) and reprogram its genetic code. With this new program, the

cells return to the stage of an embryonic stem cell, with characteristics of self-renewal and the ability to differentiate into any tissue.[29]

Later, in 2007, the first human induced cells developed from skin cells were produced. This has been so far the main source of cells for reprogramming.[30,31] This type of cell lineage brings benefits such as the ability to generate cells with different disease models, in order to study pathophysiological mechanisms and test new drugs, and without ethical conflicts such as those that occur with the use of embryonic stem cells. Another benefit is that they can be generated from the patient and possibly be used as a source for autologous cell therapy. This eliminates the risk of rejection increasing the chance of successful transplantation.[32]

Numerous healthy cell lines have been developed from induced pluripotent stem cells, such as cardiomyocytes and liver cells, and for many disease models as well, like Alzheimer's, type 1 diabetes, cerebellar ataxia, and others. Since iPSs production technique has currently been mastered, studies now focus on the safety of their use in clinical therapies.[33-37]

OTHER ADULT STEM CELL SOURCES FOR CUTANEOUS DISEASES

When it comes to treatment of cutaneous diseases, the use of cellular therapy with stem cells, regardless of the source of cells used, is still considered experimental.

Nonetheless, several clinical protocols are in progress, such as allogeneic bone marrow transplantation for recessive dystrophic epidermolysis bullosa. After results of preclinical studies showing significant improvement in the presence of collagen VII in mice, a clinical study of allogeneic stem cell transplantation demonstrated increased production of collagen VII in the host and presence of donor cells in the recipient's skin.[38] More studies are needed to monitor disease progression and assess risks and benefits of this therapy.

Comparing the hematopoietic stem cells nonablative autologous transplantation versus the traditional treatment with cyclophosphamide for systemic sclerosis, a randomized study demonstrated improvement of skin and also pulmonary function for at least two years post transplantation, when compared with conventional treatment.[39]

Autologous hematopoietic progenitor cells transplantation has been considered an experimental therapeutic alternative for systemic lupus erythematosus with systemic symptoms and those still refractory to conventional treatments. Transplantation using mesenchymal stem cells from bone marrow in autoimmune diseases like lupus have resulted in clinical remission and functional improvement of the affected organs.[40] More studies are needed for the use of these alternative therapies on a larger scale.

STEM CELLS IN CHRONIC WOUNDS

Chronic wounds can be considered an ever growing problem, since nowadays 50% of severe skin wounds do not respond to current treatments.[41] Wound healing is a complex process that requires a composition of factors equivalent that of native skin and also a coordinated interplay of extra-cellular matrix, growth factors, cells and endogenous proteins.[42]

The exogenous application of stem cells for wound healing can be considered a promising solution because of their intrinsic capacity to self-renew and differentiate into various tissues.[43] The use of stem cells in wound healing is clinically relevant, especially in those that are difficult to heal, such as lesions resulting from diabetes, major trauma, vascular insufficiency, severe and extensive burns and numerous other conditions.[42]

Mesenchymal stem cells play an important role in the remodeling of wound healing, being assigned to them paracrine factors with potential to promote improvement in the general state of a given tissue damage or injury recovery in various degrees. These paracrine effects are described as immunomodulating, anti-apoptotic, pro-angiogenic, chemo-attractor, and anti-fibrosis effects and also the support to endogenous stem cells growth and differentiation.[44,45] The presence of mesenchymal stem cells at the site of injury directs the regeneration and consequently the return of natural physiological functioning leading to regenerative success.[42]

Although bone marrow is one of the most frequently used sources for obtaining the stem cells used in cell therapy for wounds regeneration, various sources have been successfully adopted, including skin, adipose tissue, periosteum, tendons, muscle, and others. A source which recently became a target for research is the use of tissue extracted from placenta and human umbilical cord. Comparison of mesenchymal stem cells derived from bone marrow with those derived from placenta or umbilical cord tissue showed minimal differences in cellular phenotype, differentiation and other properties assigned to them.[46,47]

Mesenchymal stem cells play an important role in mediating each stage of the wound healing process. During the inflammatory phase, they can coordinate the effects of inflammation by stimulating anti-inflammatory cytokines, as well as inhibiting the deleterious effects of pro-inflammatory cytokines. This ability to promote the attenuation of inflammation is particularly critical for chronic wound treatment, in which high levels of inflammation can prevent the tissue regeneration process. Mesenchymal stem cells contribute to

the proliferative phase of regeneration through the secretion of growth factors such as VEGF, bFGF, KGF and promotion of granulation and epithelialization. These cells can also regulate remodeling of the healed wound by promoting organized extracellular matrix deposition during its replacement.[42]

The advantages of using mesenchymal stem cells for wound healing were demonstrated in various preclinical and clinical studies. Although many products are currently available to treat severe wounds, existing therapies are still inadequate in many cases, and mesenchymal stem cells are an attractive alternative to promote regeneration.

STEM CELLS AND MELANOMA

Knowledge on the pathophysiology of melanoma's origins is changing. Traditionally, it was assumed that cancer cells arose from melanocytes. Due to the presence of melanocyte precursors in the dermis, an hypothesis was formulated that melanoma could also originate in extrafollicular stem cells modified by harming factors such as UVA and UVB.[48] Therefore, mechanisms that lead to melanoma formation may occur by cellular changes in melanocytes, melanocytes'stem cell precursors or both. Experimental studies are underway to elucidate the mechanisms capable of causing damage to the DNA of stem cells, to ascertain this hypothesis.[49]

Currently, clinical trials using hematopoietic stem cells transplantation, adjuvant to chemotherapy and immunotherapy for patients with metastatic melanoma, are underway in several centers, however without definitive results.

Hematopoietic precursor cells transplant would allow the use of higher doses of chemotherapy for superior eradication of tumour cells (www.clinicaltrials.gov).

CONCLUSION

Hematopoietic stem cells have contributed directly to the health of patients currently treating hematological diseases such as leukemia and lymphoma, metabolic and immunologic disorders, besides the most prevalent solid tumors in childhood. However, its potential for the treatment of diseases that depend on significant and specialized tissue regeneration is very great and has been evidenced by the scientific community through the numerous clinical trials underway. Among these trials are researches on cutaneous diseases with systemic repercussions, showing promising results. Stem cells located in the skin have shown interesting plasticity, moreover, mesenchymal cells of the dermis, hypodermis and other sources are involved in studies to promote chronic wounds regeneration. Induced pluripotent stem cells are mostly produced using skin cells and they play an important role in the development of cell lineages that allow the study of certain diseases' pathophysiology and test new drugs.

The scientific community strives to unravel the potential diversity of stem cells present in the tissues and determine the best sources for specific diseases, and certainly skin stem cells have played an important role in this process. ❑

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